
SYSTEMATIC REVIEW OF SOCIETAL AND HEALTH SYSTEM COST OF DENGUE IN LATIN AMERICA

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ABSTRACT

Aim: to conduct a systematic literature review on dengue costs in Latin America, comparing study methodologies, disease costs and the economic impact of dengue in different countries. **Methods:** the literature search was carried out in the following electronic databases: *MEDLINE/PubMed, EMBASE and LILACS*, for the period between 2004 and 2014. To make comparisons possible, the costs identified in the selected studies were converted to local currency values, adjusted to the consumer price index (2014) and converted to purchasing power parity (PPP). **Results:** 728 publications were identified in databases and 13 papers were selected for analysis. Nine of the thirteen studies were conducted from a societal perspective and three from a health system perspective. In most studies, indirect costs accounted for the largest percentage of total outpatient costs. In contrast, for hospitalized patients, direct medical costs showed the highest percentages. The economic impact of dengue was estimated at US\$ 3.2 billion per year, ranging from US\$ 1.4 to US\$ 5.9 billion, when including the six sub-regions of the Americas. **Conclusion:** dengue represents a high cost for Latin American society and health system. Studies varied in terms of cost methodology (cost items included, such as direct medical and non-medical and indirect costs, and cost analysis) and the different epidemiological periods in which research was carried out (endemic and/or epidemic).

KEY WORDS: Dengue; costs; health economics; Latin America; review.

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INTRODUCTION

Several Latin American countries are currently facing an epidemic of three important arboviruses: dengue, Zika and chikungunya. Besides the devastating effect on the health of the population, the risk of chronicity, early deaths and congenital malformations, these diseases also bring about a major economic impact on the health system and society in general. (CDC, 2016; IVAC, 2016; Paixão et al., 2016). According to the World Health Organization (WHO), 50 to 100 million people are infected with dengue virus every year (WHO, 2009). However, new global estimates go as high as 390 million infections annually (Bhatt et al., 2013). A recent study on the distribution and impact of dengue indicated that American countries account for 40.5 million people infected and 13.3 million cases of dengue fever (Bhatt et al., 2013).

Dengue is considered one of the main public health challenges in the Americas due to the burden of the disease, the difficulty in controlling the vector and its epidemic potential (WHO, 2009; Bhatt et al., 2013; IVAC, 2016). Thus, the need for developing a vaccine to prevent dengue and the recent Zika, dengue and chikungunya epidemics in Latin America, highlights the importance of studying the economic impact of these diseases. Studies addressing cost of illness evaluate the impact of a disease and its comorbidities on the health outcomes and its effect on longevity, morbidity, decrease in health status and quality of life. Furthermore, these studies analyse financial aspects of the disease including direct and indirect expenditures due to premature death or disability. Therefore, disease cost estimates are highly relevant in regard to better allocation of resources and to support economic evaluations, such as cost effectiveness of new technologies for coping with the epidemics, and budget impact analyses used for decision making (Jo, 2014).

Drummond et al. (2005) points out that the cost and burden of disease on society, as well as the years of life lost, are key components in economic evaluations (Drummond et al., 2005; Vanni et al., 2009). However, methodological variability in the different studies could make it difficult to compare results between countries, regions and/or different epidemic periods (Suaya et al., 2009). Recently, the International Vaccine Access Center (IVAC) published a methodological guide for dengue costing studies in the Americas entitled *Costing Dengue Cases And Outbreaks: A Guide To Current Practices and Procedures* (Armien et al., 2012). These recommendations are the result of a joint effort of health researchers and healthcare managers in endemic countries to make economic studies on dengue comparable (Armien et al., 2012). A systematic review assessing the cost of dengue in dengue-endemic countries worldwide (1980-2013) reported substantial costs due to hospitalization and lost earnings and suggested further research in this area (Constenla et al., 2015).

We conducted systematic literature review of dengue cost studies in Latin America, assessing studies in accordance with published methodological guidelines (Armien et al., 2012) and comparing the economic impact of the disease in different countries. Our review focused on dengue costs in Latin America countries, calculating comparable data from 2004 to 2014.

METHODS

Literature Review, Data Selection and Extraction

A literature review of published papers on dengue costs was carried out in the following electronic databases: (1) *Medical Literature Analysis and Retrieved System* – MEDLINE/PubMED (<http://www.ncbi.nlm.nih.gov/pubmed/>); (2) EMBASE (<http://www.embase.com/login>) and (3) the *Latin American and Caribbean Center on Health Sciences Information* (LILACS) (<http://lilacs.bvsalud.org/>), as well as manual bibliographic searches from relevant review papers.

Literature research was conducted by means of descriptors recorded on the Health Sciences Descriptors (DeCS) and the Medical Subject Headings (MeSH) databases. Searches were conducted for terms present on study titles and abstracts in Portuguese, Spanish and English. Boolean operators “AND” and “OR” and quotation marks were used to facilitate the search for documents. The combination of terms used in the search were: “dengue”; “dengue virus”; “severe dengue”; “hemorrhagic dengue”; “dengue hemorrhagic fever”; “hemorrhagic fever dengue”; “dengue shock syndrome”; “classic dengue fever”; “classical dengue”; “cost”; “cost analysis”; “direct costs”; “indirect costs”; “cost measure”; “cost of illness”; “health care costs”; “health expenditure”; “burden of illness”; “cost of disease” and “cost of sickness”. Figure shows the complete strategy used in searching for papers. We included original research papers published in international or national journals. We focused on studies conducted in Latin America, published between January 1st, 2004 and October 8th, 2014. Editorials, conferences and case reports were excluded. Bibliographic references on selected papers were also reviewed to search for documents not displayed in the database search.

Two independent reviewers who read titles and summaries initially selected papers. In case of divergences, a third reviewer decided whether the article would be included. Two independent reviewers (MPPDP and NTSF) for data extraction and subsequent revision by reviewers (CMTM and FC) also read the selected papers in full. The whole group evaluated disagreements in order to reach a common ground on data collection.

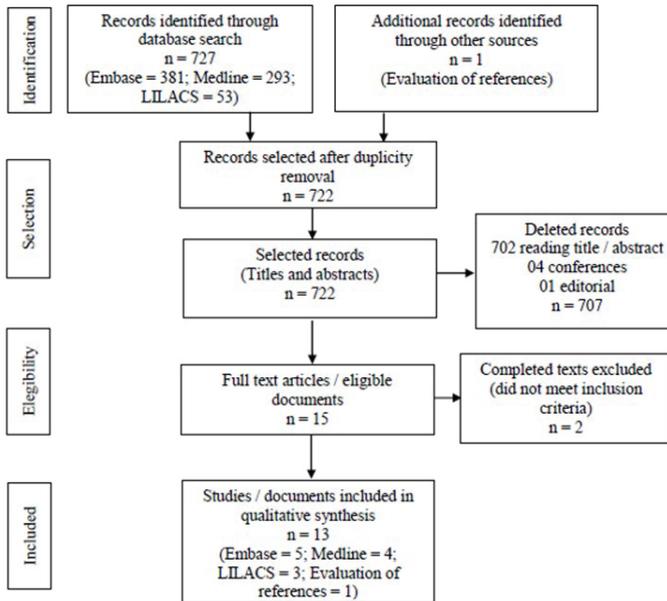


Figure. Results of the bibliographic search in the identification of dengue cost studies in Latin America

An instrument of data collection was developed for extracting data. This collection tool was based on the guide *Costing Dengue Cases And Outbreaks: A Guide To Current Practices And Procedures* (Armien et al., 2012). The choice of this guide as a model for the data collection sheet was due to the quality of its guidelines regarding dengue-costing studies, despite the fact that it was not designed specifically for systematic review purposes. The variables used were: first author (reference), year of publication, location (city, state and country), sample size, ratio of outpatient: hospital cases, study design (cost analysis, cost-of-illness, cost of outbreak), type of data (primary data, secondary data), study perspective (societal, health system), study period, expansion factor (outpatient and hospital), sensitivity analysis, cost component (direct medical and non-medical costs, indirect cost) for outpatient and inpatient. The expansion factors were those provided by the studies. We also extracted: case definition, sector (public or private), estimated regional and/or national cost, impact on country's GDP, study limitations, and inclusion of vector control program costs and social mobilization (data not shown).

Data Analysis

Each cost component was converted to local currency values for each country for the investigated year. Subsequently, the resulting monetary values were adjusted in accordance with the annual consumer price index for all urban healthcare users in 2014. This was done to account for the effects of inflation in that period. (US Department of Labor. US labor statistics data. Consumer Price Index. <http://www.bls.gov/cpi/>). Next, values were converted according to purchasing power parity (PPP), which is the exchange rate equivalent to the price of a basket of identical goods and services in different countries. Thus, direct inpatient and outpatient health system and societal costs were expressed in international dollars (I\$), which is an hypothetical unit of currency used in order to enable comparison between countries using the US dollar as a common reference. (Organization for Economic Co-operation and Development. Purchasing power parities - PPP -<http://www.oecd.org/std/ppp>). Cost conversions per episode of dengue were carried out for studies with primary data (OECD, 2014). Publications that have updated results already published were not converted to avoid duplicate information.

Direct medical (medications, tests) and non-medical (transportation, food) costs were analysed, as well as indirect costs (productivity loss and school days lost) and total cost (sum of indirect and direct costs). The result was expressed in cost per case of dengue fever, which is classified as outpatient and hospitalized cost.

Quality Assessment and Protocol Revision

The quality of selected papers was assessed according to methodological recommendations described on the *Costing Dengue Cases And Outbreaks: A Guide To Current Practices And Procedures* (Armien et al., 2012). The quality assessment was focused on the methods and analysed seven criteria described in the guideline. (1) Perspective of analysis: patient/family, provider or societal perspective. The guideline recommends the adoption of the broader societal perspective, with the inclusion of all types of health care providers. (2) Time frame: epidemic and non-epidemic period. The recommendation is to perform the costing study covering both epidemic and non-epidemic periods, as a short period of analysis would not capture variation in costs due to inter-epidemic intervals and seasonal fluctuations. (3) Definition and classification criteria of cases: dengue with and without warning signs and severe dengue. This item is important because it allows the comparison of costs among different types and degrees of severity of dengue disease. (4) Sample size and sample rate calculation: method description and sample representativeness in terms of the study population. This allows the assessment of the representativeness of costs ensuring that the empirical estimate is close to the true value in the

population under analysis. (5) Cost category: (hospitalized or outpatient), with the guideline recommending the adoption of both categories (6). Classification of costs: direct medical and non-medical costs, indirect costs. The guideline recommends the inclusion of all costs involved in the diagnosis and treatment of dengue in order to have a better understanding of the main contributors to the total cost and its dynamic. (7) Data sources: primary data collection - prospective and retrospective, interviews; secondary data collection - published literature, national data. The systematic review protocol was not registered in any systematic review database.

RESULTS

Selection and Paper Characteristics

In total, 728 publications regarding the costs of dengue were found, of which 13 papers met the inclusion criteria for the study (Figure 1). Out of all papers included, five came from the EMBASE database; four from MedLine (PubMed); three from LILACS and one from the manual bibliographic search. Of the 20 countries in Latin America, only half of them have measured the economic impact of dengue. Eleven of thirteen publications refer to studies conducted in the following countries: Argentina (1 paper), Brazil (2 papers), Colombia (1), Cuba (2), Nicaragua (1) Panama (1), Puerto Rico (1) and Venezuela (2). Suaya et al. (2009) and Shepard et al. (2011) conducted multicenter studies including several countries in the Americas (Brazil, El Salvador, Guatemala, Mexico, Panama and Venezuela). Publications by Armien et al. (2008) and Suaya et al. (2009) use primary data from one same study to estimate dengue costs in Panama.

Table 1 shows the main characteristics of selected studies. Nine of the thirteen studies were conducted from a societal perspective and three from the health system perspective (public and/or private). The expansion factor (EF) for outpatient and hospitalized cases was used in five studies, but there is large variation between the EF used. This measure is used to adjust the number of dengue cases reported by official health information systems in order to get a more realistic estimate (Undurraga et al., 2013). The highest EF values were recorded for studies in Nicaragua (Wettstein et al., 2012), which assigned an EF value of 20 for the endemic period and 10 for the non-epidemic period. The multicenter study (Suaya et al., 2009) conducted sensitivity analyses with EF variation (2, 3 and 6).

Table 2 shows direct medical and non-medical costs and indirect costs per patient converted to international dollars (2014), divided into outpatient and hospitalized. The cost per dengue case varied greatly in Latin America studies. Two studies of dengue hospitalization costs were performed in Venezuela. Both assessed direct medical costs and one of them also evaluated indirect costs (Añez et al., 2006; Natera et al., 2009). The first study showed that the

direct medical cost of hospitalized dengue patients was I\$ 137, and indirect costs ranged from I\$ 402 to I\$ 525 for the years 2001 and 2003, respectively. In the second study, direct medical cost estimates for the capital Caracas ranged from I\$ 1,244 to I\$ 3,066 for the years 2000 and 2008, respectively (Natera et al., 2009).

In Argentina, the study by Tarragona et al.(2012) evaluated dengue hospital costs in three scenarios during the 2009 outbreak, with lower-cost (first scenario) and higher-cost (third scenario) medical alternatives for patients treated in intensive care units (ICU) in different regions of the country. Direct medical costs ranged from I\$ 242 to I\$ 872 (ICU) and indirect costs ranged from I\$ 277 to I\$ 320 for labour loss and from I\$ 24 to I\$ 35 for school days lost, depending on the region (Tarragona et al., 2012).

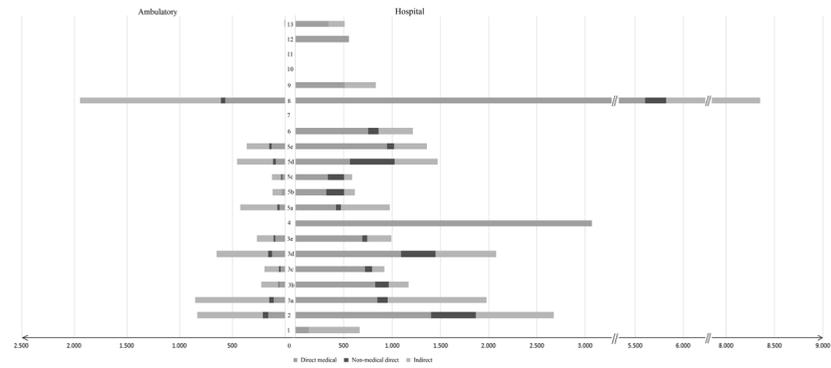
In Guantanamo, Cuba, dengue hospital cost was estimated at I\$ 1,213. The direct medical cost was I\$ 752, which represents ~62% of the total, followed by the indirect cost: I\$ 352 (~29%) (Baly et al., 2012). A study undertaken in two cities of Colombia estimated that severe dengue cases had costs of more than 60% compared to less severe hospitalized cases (I\$ 2,031 versus I\$ 1,283) (Castañeda-Orjuela et al., 2012). Valdés et al. (2012) carried out a partial economic evaluation for hospitalized dengue cases during an epidemic period in Santiago de Cuba, where the total costs for hospitalization showed 79.8% of direct medical costs (Valdés et al., 2012).

In Puerto Rico, Halasa et al. (2012) evaluated the outpatient and hospital costs of dengue fever. The cost of a dengue episode for outpatients was I\$ 1,944, of which approximately 70% accounted for indirect costs and 30% for direct medical and non-medical costs. For hospitalized patients, about 70% of total costs were direct medical costs. Hospital costs were about four times higher than outpatient costs (Halasa et al., 2012). In Nicaragua, the total cost per patient, both outpatient and hospital, ranged from I\$ 373 to I\$ 797 (Wettstein et al., 2012).

Machado et al. (2014) conducted a study in a public hospital and three private hospitals in the city of Dourados, Mato Grosso do Sul (MS), in the Midwest region of Brazil. This work estimated direct medical costs at I\$ 554 (Machado et al., 2014). The study by Pereira et al. (2014) evaluates dengue episode costs after the 2011 floods in the city of Nova Friburgo, state of Rio de Janeiro. Direct medical costs were estimated at I\$ 342 and indirect costs ranged between I\$ 97 and I\$ 166, according to the national minimum wage (2011) and the city's average income, respectively. In this study, the authors show an increase of at least 30 times in the number of reported dengue cases after this environmental disaster, compared to previous years (Pereira et al., 2014).

In the multicenter study by Suaya, Castaneda-Orjuela and Halasa, the total hospital cost was higher than outpatient cost. Hospital costs varied from I\$ 8,355 to I\$ 917 for Puerto Rico and Guatemala, respectively. The direct medical costs component accounted for approximately 70% of the total cost, except for Brazil (~ 50%). The total cost for outpatients showed inter-country variation from I\$ 1,944 to I\$ 193 for Puerto Rico and Guatemala, respectively. The conversion table of dengue cost components to international dollars did not include publications by Armien (Panama) and Shepard (multicenter), whose results were in the publication by Suaya et al. (2009).

Graph summarizes cost components of a dengue episode for outpatients and hospitalized patients. Most studies reported outpatient costs. Hospitalization cost was the biggest cost component in the cost of dengue treatment in all selected studies. For ambulatory cases, indirect cost was the main component of total costs. In contrast, for hospitalized patients, direct medical cost was the main component of the total costs.



Graph. Cost of dengue (International dollars, I\$) by ambulatory and hospital according to the studies selected, Latin America (2004-2014).

Table 1. Main Characteristics of Dengue Costing Studies in the Americas, 2004 to 2014.

Reference	Country	Sample Size	Ratio of Outpatient:Hospital Cases	Study design	Type of data	Study Perspective	Study Period	Outpatient EF	Hospital EF	Sensitivity Analysis
Añez et al., 2006	Venezuela	-	-	Cost of illness	Primary and secondary data (surveillance system)	Societal	1997-2003	-	-	-
Arminen et al., 2008	Panama	136	1:0.05	Cohort Cost of the 2005 epidemic QUALY	Primary data	Societal	2004-2005	6	6	Univariate (EF 1-10)
Suaya et al., 2009 ^a	Brazil	550	3:1	Multicenter Cohort	Primary data	Societal	2005	3	3	Univariate (EF 2, 3, 6)
	El Salvador	189	1:1							
	Guatemala	85	3:1	Cost analysis	Primary data	Societal	2005	3	3	
	Panama	136	1:0.05							
	Venezuela	200	2:1							
Natera et al., 2009	Venezuela	453	0:1	Descriptive prospective study Cost analysis	Primary data	Health system	2000-2008	-	-	-

Shepard et al., 2011 *	North America, Central America, Andes Region and Mexico, Brazil and the South Cone, Caribbean Region	-	-	multicenter cohort Cost analysis	Secondary data	Societal	-	Nicaragua EF=20.4 Panama EF=6 Puerto Rico and other countries EF=15	Colombia and Nicaragua EF=2,3 Puerto Rico EF=2,4 Other countries EF=2,3	Brazil EF = 1.6	Probabilistic, Monte Carlo simulation
Baly et al., 2012	Cuba	3549	0:1	Cost of outbreak and non-epidemic period	Primary and secondary data	Societal	2006	-	-	-	-
Castaneda-Orjuela et al., 2012	Colombia	271	-	Retrospective study		Public payer	-	-	-	-	-
Halasa et al., 2012	Puerto Rico	100	1:2	Prospective study Cost of illness	Primary and secondary data	Societal	2008-2010	10	2.42		Outpatient EF between 5 and 27
Tarragona et al., 2012	Argentina	201	10:1	Cost of outbreak	Primary and secondary data	Societal	2009	-	-	-	-
Valdés et al., 2012	Cuba	22,196	0:1	Descriptive and retrospective study	Secondary data	Health system	2006-2007	-	-	-	-

Wetstein et al., 2012	Nicaragua	Lab-confirmed dengue cases between 1996-2010 Suspected cases between 2004 and 2010	-	Cost of illness	Secondary data	Societal	1996-2010	Endemic period EF = 20 (variation 18-25) Epidemic period FE = 10 cases DF (variation 8-14) DHF cases EF = 6 (variation 5-10)	Probabilistic (Monte Carlo simulation), univariate
Machado et al., 2014	Brazil	288	0.1	Retrospective study	Secondary data	Health systems (public and private)	2010	-	-
Pereira et al., 2014	Brazil	1356	93.7	Cost of illness	Secondary data	Societal	2011	-	-

EF: Expansion factor * Multicenter study

Table 2. Cost components for outpatient or hospital dengue case, according to studies and countries, in international dollars (\$, 2014)

Reference	Country	Outpatient		Hospital			Total cost	
		Direct medical	Direct non-medical	Indirect	Direct medical	Direct non-medical		Indirect
Suaya et al., 2009 ^a	Brazil	109	39	706	849	106	1025	1979
	El Salvador	57	5	162	828	135	207	1171
	Guatemala	41	17	134	717	77	124	917
	Panama	122	39	487	1,092	359	628	2079
	Venezuela	95	15	156	694	50	249	994
Añez et al., 2006	Venezuela				137			525 – 402 ^b
Natera et al., 2009	Venezuela				1,244 – 3,066 ^c			
Tarragona et al., 2012	Argentina				242 – 872 ^d			277 – 320 ^e
Baly et al., 2012	Cuba				752	109	352	1213
Castaneda-Orjuela et al., 2012	Colombia			138				1283 ^f 2031 ^g
Halasa et al., 2012	Puerto Rico	570	36	1,338	5,604	219	2532	8355
Wetstien et al., 2012	Nicaragua				554			373 – 797 ^h
Machado et al., 2014	Brazil							
Pereira et al., 2014	Brazil	8			342			97 – 166

^aMulticenter study; ^b Indirect costs per dengue episode evaluated in 2001 and 2003, converted to 2014 \$.

^c Direct medical costs per hemorrhagic dengue episode evaluated in 2000 and 2008, converted to 2014 \$.

^d Variation between lower and higher direct medical costs; ^e Variation of indirect costs related to labor loss

^f hospital cases; ^g severe cases; ^h Variation of the total cost, outpatient and hospital

Table 3. Quality appraisal of the retrieved studies: Costing Dengue Cases and Outbreaks: A Guide to Current Practices and Procedures

References	Adoption of Societal perspective?	Time horizon covering epidemic and non-epidemic periods?	Definition and classification criteria of cases described?	Sample size and rate calculation described?	Cost category described and adoption of inpatient and outpatient category?	Classification of costs described and inclusion of all costs, direct and indirect?	Source of data collection described?
Añez et al, 2006	Yes	Yes	No	No	No	No	Yes
Armien et al, 2008	Yes	No	Yes	No	Yes	Yes	Yes
Suaya et al, 2009 *	Yes	Yes	Yes	No	Yes	Yes	Yes
Natera et al, 2009	No	Yes	Yes	Yes	No	No	Yes
Baly et al, 2012	Yes	Yes	No	No	No	Yes	Yes
Castaneda-Orjuela et al, 2012	No	Yes	No	Yes	Yes	No	Yes
Halasa et al, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tarragona et al, 2012	Yes	No	No	Yes	No	No	Yes
Valdés et al, 2012	No	No	No	No	No	Yes	Yes
Wettstein et al, 2012	Yes	Yes	Yes	No	No	No	Yes
Machado et al, 2014	No	No	Yes	Yes	No	No	Yes
Pereira et al, 2014	Yes	No	No	No	Yes	No	Yes
Proportion of studies meeting the Guideline's criteria	67	58	50	42	42	42	100

Quality Assessment

Only the study by Shepard et al. (2011) did not carry out a quality assessment because it was a systematic literature review. For this type of study, other quality assessment methods must be applied. The quality assessment identified that most studies were carried out from a societal perspective 67% (8/12). Four studies considered provider perspective. Most of them 58% (7/12) also covered both the epidemic and non-epidemic periods and all of them reported data collection sources adequately. Other quality aspects were also assessed and the conclusion was that most studies did not follow the criteria established by the reference guide. These quality aspects were the following: a) criteria for defining and classifying reported cases (6/12); b) sample size calculation with method description and representativeness of sample according to study population (5/12); c) description of outpatient and hospital cost categories (5/12) and; d) description of cost classification (direct medical and non-medical costs and indirect costs) (5/12). Table 3 gives a detailed description of the quality assessment.

DISCUSSION

In the Americas the first multicenter study from a societal perspective was undertaken simultaneously in five countries (Brazil, Venezuela, El Salvador, Guatemala, Panama) in 2005 (Suaya et al., 2009). The total cost per outpatient and hospital episode showed inter-country variation. Indirect costs accounted for the largest percentage of the total outpatient cost. For hospitalized dengue patients, the greatest part of the total costs was direct medical costs. Considering that the study used a common research protocol, variability in cost per episode of dengue appears to reflect differences in local healthcare provision, type of healthcare access and economic conditions of each country. The authors estimated a total of I\$ 343 million in aggregate morbidity and mortality costs due to dengue (2001-2005) in these five American countries. In another study (Shepard et al., 2011) the economic impact of dengue was estimated at I\$ 3.2 billion per year, ranging from I\$ 1.4 to I\$ 5.9 billion, when including six sub-regions of the Americas: North America (United States and Canada); Central America and Mexico; Andes region (Bolivia, Colombia, Ecuador, Peru, and Venezuela); Brazil and the South Cone (Argentina, Chile, Paraguay and Uruguay); and the Caribbean. This update of the economic impact of dengue used cost results from the multicenter study (Suaya et al., 2009) updating values for 2010 and transferring them to other countries in the region.

The multicenter study conducted in different countries of the Americas made it possible to compare direct and indirect costs of a disease episode in different regional epidemiological contexts (Suaya et al., 2009). In this study,

the average cost per hospitalized case was estimated at approximately I\$ 1,700 in Panama and Brazil versus I\$ 750 in Guatemala. Intra-country comparisons showed that the average cost per hospitalized case was about three times higher than the cost of an outpatient case. In outpatient cases, indirect costs caused by productivity loss for patients and families and school days lost were higher than the direct medical costs. In this study, Brazil was represented by a capital city in the Midwest region and the research was carried out in 2005, with circulation of DENV-1, DENV-2 and DENV-3, before the rise of dengue transmission in the region.

After the period addressed by this review (2014), recent publications on the impact of dengue in Colombia (Rodriguez et al., 2015), México (Undurraga et al., 2015) and Brazil (Martelli et al., 2015) should also be discussed. The cost of dengue in Colombia was estimated at approximately US\$ 168 million in the 2010 epidemic (Rodriguez et al., 2015). In this study, direct medical costs of a dengue episode accounted for most of the total costs of hospitalized patients while indirect costs associated with patient or caregiver production loss accounted for the largest share of costs per outpatient case. This proportional distribution of cost components was similar to that found in previous studies in other countries of the Americas (Shepard et al., 2011; Suaya et al., 2009).

Recently, a study of dengue burden in Mexico evaluated disease and prevention costs using multiple data sources (Undurraga et al., 2015). In addition to the DALY burden of disease, a sensitivity analysis of other parameters was also undertaken (expansion factor, unit costs, days of work lost, use of health services, among others) to assess possible uncertainties of economic estimates. Estimates broken down by cases and deaths were presented for the period between 1995 and 2011. In Mexico, the average annual cost of dengue was estimated at US\$ 170 million.

In Brazil, the overall cost of dengue from a societal perspective reached US\$ 1.2 billion in the 2012-2013 epidemic (Martelli et al., 2015). These high values include medical costs, productivity loss and deaths considering adjustments of reported cases. We believe that this national multicenter study was the most representative dengue impact evaluation from a societal perspective using data from interviews of about two thousand suspected cases of dengue, both outpatients and/or hospitalized, in the public and private sector, and covering the four most endemic areas in the country (North; Northeast, Midwest and Southeast). The cost of a dengue episode showed inter-region variation depending on the type of health services provided, the incidence and/or severity of the disease, the proportion of public and private sector healthcare provision and the population's socioeconomic status. In this study, 67% of the total costs were related to outpatient costs. Thus, dengue had a significant economic impact, especially due to the great demand for outpatient care and disease-related productivity loss. Although the average cost of a hospitalized dengue case was greater than the outpatient cost. Only 10% of all dengue

cases were hospitalized in the studied period (Martelli et al., 2015). Overall, productivity loss has been identified as one of the main cost components of dengue measured as an indirect cost component, which reinforces the need to assess the impact of dengue from a societal perspective (Constenla et al., 2015; Undurraga et al., 2015; WHO, 2009).

It is worth noting the variability in dengue episode costs among different American countries as well as within the same country. This is true even for multicenter studies using the same research protocol (Suaya et al., 2009). Different inclusion criteria for cases (suspected and/or confirmed by lab test) can affect the disease cost, which makes it difficult to compare the impact of the disease.

Estimates of the overall costs of dengue depended on records of dengue cases reported by surveillance systems (Shepard et al., 2011). Epidemiological aspects, such as disease seasonality (endemic and epidemic periods) and characteristics of surveillance systems should be taken into account when interpreting the overall cost estimates (Runge-Ranzinger et al., 2014; Stahl et al., 2013). For example, in Brazil, dengue is characterized by a growing time series trend with a wide geographical dispersion between 2000 and 2010 (Teixeira et al., 2013). About one million cases of dengue were reported in 2010, while two million cases were recorded in the epidemic of the year 2013 (Brasil, 2013).

For dengue economic impact studies, it is recommended to include epidemic and endemic periods and a wide time frame (years) in order to compare different periods (WHO, 2009). Three studies included in our systematic review included cost of illness for outbreak (Armen, Baly, Tarragona). This strategy has been applied in several costing studies that include a historic series of cases reported for national cost assessments (Martelli et al., 2015; Undurraga et al., 2015). In order to adjust the data regarding notifications of the passive surveillance system, an expansion factor is used, which is the ratio between existing symptomatic cases of dengue fever and the number of cases registered by the notification system. In general, the EF for outpatient cases is greater than the EF for hospitalized cases. In addition, there are variations between endemic and epidemic periods. A recent review of EFs that quantify underreporting of dengue in surveillance systems of different endemic countries showed an information gap in Brazil (Toan et al., 2015). Our systematic review identified six studies that used EF to adjust for underreporting an important issue in many dengue-endemic countries. Different expansion factors are chosen for outpatient and inpatient, sometimes based on literature or expert opinion. The huge variation between EF shows there is little agreement between experts on the value to be used to adjust for missing cases.

In conclusion, our systematic review showed that dengue represents a high cost for Latin American health systems and society. The costs of dengue episodes varied among different studies, due to the characteristics of

surveillance systems in each country, and to whether studies were carried out in endemic or epidemic periods. Methodological variability makes it difficult to compare studies between countries/regions and/or in different epidemic periods. Differences were observed across economic studies: design, data sources, cost components and outcomes measured and dengue case definition. Few costs studies included surveillance costs (Tarragona, Baly). As mentioned by Constenla et al (2015) “there is a need for standardized guidelines describing appropriate sources, minimum cost components and use of proxy cost estimates when data are not available from the country or region under analysis”. In general, school absenteeism and productivity loss represented a significant portion of dengue episode costs. Moreover, if one considers the dynamic characteristics of dengue epidemiology in the Americas, other economic studies regarding this disease are also recommended.

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